



# Comparative Effectiveness Research at the FDA: Taking the “Person” out of Personalized Medicine?

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**COMPARATIVE EFFECTIVENESS RESEARCH AT THE FDA:  
TAKING THE “PERSON” OUT OF PERSONALIZED MEDICINE?**

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This paper is submitted in satisfaction of the course requirement.

## **ABSTRACT**

Since the advent of genetic databases in the 1990's, personalized medicine (PM) has been heralded as the future of medical treatment. Although the expected revolution has been more of a slow and arduous journey, the FDA has put forth significant effort to pave the way for PM techniques in the approval process. The nascent field has recently been threatened, however, by an unprecedented apportionment of federal funds to comparative effectiveness research (CER), a government project aimed at enhancing efficiency in federal spending by assessing the relative effectiveness of available treatment options across populations. A great deal of literature attempts to predict the likely impact of CER, which is intended to study effectiveness among populations or subgroups, and PM, which focuses on effectiveness in the individual. The general consensus is that the impact will be a positive one, with both strategies mutually enhancing the quality of medical treatment for each individual. Few have expounded upon the effects of CER on PM at the FDA in particular, however. This paper explores some of the ways in which CER may interact with the FDA's stated goal of furthering PM. It concludes that in spite of certain practical limitations on the symbiotic coexistence of PM and CER, CER is unlikely to obstruct the FDA's pursuance of PM.

## I. INTRODUCTION

Last year, lung cancer diagnosis was a death sentence for 159,390 Americans.<sup>1</sup> Due to AstraZeneca's revolutionary drug Iressa, however, approximately ten percent of patients diagnosed with non small cell lung cancer have hope. A fortunate few possess a natural advantage: a mutation in the DNA coding sequence for a protein called epidermal growth factor receptor. Iressa binds selectively to this mutated protein, inhibiting the spread and growth of tumors without the devastating effects of chemotherapy.<sup>2</sup> The drug obtained Food and Drug Administration (FDA) approval in 2003 and has since been used to treat lung cancer in over 300,000 patients.<sup>3</sup>

As technology advances, such targeted drugs are becoming more common. Although the field is still nascent, so-called personalized medicine (PM) may soon revolutionize drug development and diagnostics by tailoring medical treatment to the wants, needs, and even the genome of the individual. Janet Woodcock, the director of the Center for Drug Evaluation and Research at the FDA, ardently champions PM as "the future."<sup>4</sup>

Accordingly, the FDA has made significant strides towards the implementation of PM in medical product development.<sup>5</sup> FDA's boldest move has been the establishment of a framework for voluntary data submission under the Guidelines for Industry on

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<sup>1</sup> See National Cancer Institute, <http://www.cancer.gov/cancertopics/types/lung> (last visited Mar. 6, 2010).

<sup>2</sup> See Iressa, <http://www.iressa.com/> (last visited Mar. 6, 2010).

<sup>3</sup> See *id.*

<sup>4</sup> Janet Woodcock, *The Prospects for "Personalized Medicine" in Drug Development and Drug Therapy*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 164, 169 (2007).

<sup>5</sup> Michael Rugnetta, *FDA Embraces Personalized Medicine*, SCIENCE PROGRESS, Feb. 6, 2009, <http://www.scienceprogress.org/2009/02/fda-embraces-personalized-medicine/> (last visited Apr. 8, 2010).

Pharmacogenomic Data Submissions (the guidelines).<sup>6</sup> The submissions are intended “to help identify sources of inter-individual variability in drug response (both effectiveness and toxicity)”<sup>7</sup> with the ultimate goal of gathering data to “individualize therapy with the intent of maximizing effectiveness and minimizing risk.”<sup>8</sup> They also indicate a process by which companies can qualify biomarkers<sup>9</sup> for clinical use.<sup>10</sup> In addition, the Critical Path Initiative (CPI), designed to enhance efficiency in product development, has a special focus on the individualization of medical care.<sup>11</sup> The guidelines have inspired a number of subsequent initiatives, including a review group for pharmacogenomic data submissions, a trial process for qualification of biomarkers, and a preliminary FDA publication summarizing discussions of the submission process.<sup>12</sup> To coordinate these efforts, a position was created for a Senior Genomics Advisor in February 2009.<sup>13</sup> In addition to their contributions to the industry, many FDA officials are responsible for a

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<sup>6</sup> U.S. DEP’T OF HEALTH AND HUMAN SERVICES, ET AL., GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS (2005), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf>.

<sup>7</sup> *Id.* at 2.

<sup>8</sup> *Id.*

<sup>9</sup> The Guidelines define a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” *Id.* at 17, citing Biomarkers Definitions Working Group, *Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework*, 69 CLINICAL PHARM. & THERAPEUTICS (2001).

<sup>10</sup> See DEP’T OF HEALTH AND HUMAN SERVICES & U.S. FOOD AND DRUG ADMINISTRATION, THE CRITICAL PATH INITIATIVE 8 (2009), *available at* <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UCM186110.pdf>.

<sup>11</sup> See Critical Path Initiative: Frequently Asked Questions, <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm077015.htm> (last visited Mar. 6, 2010).

<sup>12</sup> See Federico Goodsaid & Felix W. Frueh, *Implementing the U.S. FDA Guidance on Pharmacogenomic Data Submissions*, 48 ENVIRONMENTAL AND MOLECULAR MUTAGENESIS 354, 354 (2007).

<sup>13</sup> See Kathryn Foxhall, *FDA Creates New Genomics Position*, MEDSCAPE TODAY, Feb. 6, 2009, <http://www.medscape.com/viewarticle/587963> (last visited Apr. 9, 2010).

vast body of scholarship on the topic.<sup>14</sup> In light of all these efforts, it would not be a stretch to say that in the field of PM, perhaps the FDA has already exceeded the science itself.<sup>15</sup>

Although these initiatives are relatively new, their scope and magnitude demonstrate the FDA's strong commitment to PM. Unfortunately, recent legislation mandating the apportionment of \$1.1 billion to comparative effectiveness research (CER) has raised concerns that PM may be reduced to a passing fad.<sup>16</sup> Stated simply, the goal of CER is to compare the "real-world" effectiveness of available "health care treatments and strategies."<sup>17</sup> The funding was allocated under the 2009 American Recovery and Reinvestment Act (ARRA), which also established a Federal Coordinating Council (FCC) for Comparative Effectiveness Research for the purpose of overseeing federal spending on the project.<sup>18</sup> This unprecedented federal investment in CER has raised the ire of many PM advocates, who are concerned that such studies will only yield data about appropriate medical treatment for large populations, or at best for easily identifiable subgroups.

Will the advent of CER hinder the FDA's stated goal of advancing PM?

Advocates of both frameworks are actively working to coordinate the two approaches,

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<sup>14</sup> See Genomics at FDA – Publications by FDA Staff, <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085426.htm> (last visited Mar. 6, 2010).

<sup>15</sup> Most commentators are in agreement that the field of PM is still in an early stage. See e.g., Muin J. Koury et al., *Comparative Effectiveness Research and Genomic Medicine: An Evolving Partnership for 21<sup>st</sup> Century Medicine*, 11 GENETICS IN MEDICINE 707, 708 (2009) (noting that most known genetic variants have little clinical utility). Moreover, the guidelines up until this point have largely served as a forum for debate about the future shape of clinical trials in the era of personalized medicine. See Goodsaid, *supra* note 12, at 354.

<sup>16</sup> See The American Recovery and Reinvestment Act, 42 U.S.C. §229b-8 (2009).

<sup>17</sup> FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, RESEARCH REPORT TO THE PRESIDENT AND THE CONGRESS 5 (2009), available at <http://www.hhs.gov/recovery/programs/cer/cerannualrpt.pdf> (last visited Mar. 7, 2010).

<sup>18</sup> See 42 U.S.C. §229b-8.

which, according to a recent statement by Janet Woodcock, are “synergistic.”<sup>19</sup> This paper will discuss some of the most prevalent differences and similarities between the two strategies that have been identified in the literature, and will then make a prognosis for how these differences will play out on a practical level for the FDA.

## II. DEFINITIONS

According to the text of the ARRA, the purpose of CER is to “accelerate the development and dissemination of research assessing the comparative effectiveness of health care treatments and strategies.”<sup>20</sup> In furtherance of this goal, the FCC is instructed to:

1. Conduct, support, or synthesize research that compares the clinical outcomes, effectiveness, and appropriateness of items, services, and procedures that are used to prevent, diagnose, or treat diseases, disorders, and other health conditions; and
2. encourage the development and use of clinical registries, clinical data networks, and other forms of electronic health data that can be used to generate or obtain outcomes data.<sup>21</sup>

PM is a much more nebulous concept, indirectly implicated in several FDA regulations but never explicitly defined. Congress has offered a recent articulation of PM in H.R. 6498: “[t]he application of genomic and molecular data to better target the delivery of health care, facilitate the discovery and clinical testing of new products, help determine a person's predisposition to a particular disease or condition, and identify any targeted prevention strategies for that predisposition.”<sup>22</sup>

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<sup>19</sup> Gregory Twatchman & Mary Houghton, *Pink Sheet – CER and Personalized Medicine are “Synergistic” – FDA’s Woodcock*, FRIENDS OF CANCER RESEARCH, 2009, <http://www.focr.org/pink-sheet-cer-and-personalized-medicine-are-qsynergistic-q-fdas-woodcock.html> (last visited Apr. 7, 2010).

<sup>20</sup> 42 U.S.C. §229b-8.

<sup>21</sup> *Id.*

<sup>22</sup> Genomics and Personalized Medicine Act of 2008, H.R. 6498, 110<sup>th</sup> Con. §2(2).

Based solely on the plain language of the legislative definitions, a plausible conclusion is that Congress was simply implementing the goals of PM in its mandate to the FCC regarding CER. Both are directed towards the accumulation of information which will enhance health outcomes on an individualized basis. At the highest level of generality, both PM and CER are directed towards promotion of the public health. More specifically, Congress envisions both strategies as involving a broad array of treatment options, including drugs, devices, and strategies. Finally, both require (explicitly and implicitly) an infrastructure for the accumulation of health care data.

The similarities are highlighted in the FCC's report to the President and the Congress in June 2009 (2009 report).<sup>23</sup> In this report, the FCC interpreted its directive as requiring that CER "inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances."<sup>24</sup> The entire report is replete with language about the patient as an individual, emphasizing the patient-centered approach to CER studies.<sup>25</sup>

Thus at first blush, the two regimes do not appear to be significantly different from a Congressional perspective. However, as with all legislative enactments, under the surface many complex and conflicting considerations exist. The following analysis discloses some of the theoretical differences and similarities between PM and CER that have been expounded in the literature and offers a brief critique of these theories.

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<sup>23</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17.

<sup>24</sup> *Id.* at 16.

<sup>25</sup> *Id.*



### III. THEORETICAL COMPARISON

#### A. Person v. Group

One of the most prominent concerns about the compatibility of CER with PM is that CER is aimed at determining effectiveness across entire populations, while PM is focused on finding the best medical treatment for individuals. The FCC's concession to PM advocates from the 2009 report effectively ignores this conflict, and attempts to alleviate concerns about the de-personalization of medicine by incorporating subgroup analysis into the CER framework.<sup>26</sup> Its concession, however, overlooks the problem: a group does not cease to be a group by virtue of its small size or shared characteristics.

Nonetheless, the apparent distinction between subgroup and individual may only be semantic. As long as CER studies are capable of defining the correct groups for which a given medical treatment is effective, then the distinction between group and individual collapses.<sup>27</sup> Grouping individuals into subgroups only frustrates the goals of PM when subgroups are ill-defined. A good analogy is that of cultural stereotypes. Society objects to such stereotypes because they are often inaccurate and overbroad, thus encouraging people to make incorrect assumptions about individuals which comprise them. However, if a stereotype of a certain group of individuals is an accurate description of all individuals within the group, then there are no problems with applying characteristics of the stereotype to the individual. Similarly, if CER is able to precisely identify all

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<sup>26</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 24 (“At the same time that CER is being used to identify which interventions and strategies work best on average, it can also help to identify different responses by different groups of patients.”).

<sup>27</sup> See CLIFFORD GOODMAN, THE LEWIN GROUP, COMPARATIVE EFFECTIVENESS RESEARCH AND PERSONALIZED MEDICINE: FROM CONTRADICTION TO SYNERGY 25 (2009), *available at* [http://www.lewin.com/content/publications/Lewin\\_CER-PM.pdf](http://www.lewin.com/content/publications/Lewin_CER-PM.pdf).

subgroups relevant for a particular treatment, then the patient's treatment is properly tailored to the individual's needs.

### **B. Prospective v. Retrospective**

To date, many developments in personalized medicine have been made retrospectively, through lengthy observation of clinical outcomes after a medical product or strategy has been released onto the market. The typical PM success story is that of an approved drug with a curious pattern of effectiveness, whose clinical trial data eventually accumulates to demonstrate special success in a particular subgroup.<sup>28</sup> In contrast, CER studies are designed to predict effectiveness in patients *a priori*, skipping over the years of clinical observation that are generally a prerequisite for advances in PM.<sup>29</sup>

Nonetheless, the heretofore retrospective nature of PM may not be an intrinsic quality of this strategy. Quite to the contrary, advocates of PM aspire to make it more prospective by reducing the luck element to an exact science.<sup>30</sup> CER endangers PM only if prospective studies are incapable of identifying relevant subgroups and producing accurate results at the subgroup level, absent large amounts of clinical data.<sup>31</sup> In other words, CER comes into conflict with PM only if research in furtherance of PM is necessarily retrospective by nature.

Furthermore, the second goal of CER – involving the collection of clinical data – evidences a realization that certain discoveries can only be made retrospectively, upon

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<sup>28</sup> See e.g., Ken Garber, *Trial Offers Early Test Case for Personalized Medicine*, 101 JCN NEWS 136 (2009) (describing several targeted cancer drugs whose individualized properties were only discovered upon retrospective analysis of clinical data).

<sup>29</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17.

<sup>30</sup> See e.g., Janet Woodcock, *The Prospects for "Personalized Medicine" in Drug Development and Drug Therapy*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 164, (2007) at 164.

<sup>31</sup> See GOODMAN, *supra* note 27, at 7-9.

observation of years of data from a wide array of patients. Thus CER incorporates both prospective and retrospective elements.

### **C. Financial considerations**

While both strategies are aimed at the enhancement of medical efficiency, CER is more concerned with financial efficiency. For evidence of a financial incentive driving CER, one need only look to the context in which the recent federal stimulus for CER was apportioned: the ARRA. The ARRA's website stipulates that "while many of Recovery Act projects are focused more immediately on jumpstarting the economy, others, especially those involving infrastructure improvements, are expected to contribute to economic growth for many years."<sup>32</sup> Looking at the stimulus package as a whole, it seems impossible to view CER as anything but a government investment, and the government would not make a \$1.1 billion investment without any expectation of financial gain. Furthermore, as noted above, the 2009 report cites inefficient Medicare spending as one of the primary motivators of CER, indicating that even the FCC, in using the funds apportioned by the act, has financial considerations in mind.<sup>33</sup>

The ARRA and the 2009 report expressly disavow the use of information from CER studies for making financial decisions about insurance coverage in either the public or private sector.<sup>34</sup> Nonetheless, there is widespread concern that the research will be used to limit insurance coverage for medications that do not benefit the majority of patients, particularly under the proposed national health care plan.<sup>35</sup>

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<sup>32</sup> Recovery.gov, [http://www.recovery.gov/About/Pages/The\\_Act.aspx](http://www.recovery.gov/About/Pages/The_Act.aspx) (last visited Mar. 7, 2010).

<sup>33</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 11.

<sup>34</sup> See Section 804 of the ARRA.

<sup>35</sup> See e.g., AMERICAN ACADEMY OF ACTUARIES, HEALTH INSURANCE COVERAGE AND REIMBURSEMENT DECISIONS: IMPLICATIONS FOR INCREASED COMPARATIVE EFFECTIVENESS RESEARCH (2008), *available at* <http://www.actuary.org/pdf/health/comparative.pdf>.

In contrast, PM emerged from an academic, scientific background. The term was coined in the late 1990's with the explosion of discoveries about the human genome and the effects of its diversity on drug response.<sup>36</sup> Certainly large amounts of PM studies are funded with government money, such as NIH grants, and the strategy is generally thought to reduce the cost of medical care. Its origins are simply less suspect since it arose from scientific discovery and is typically not championed as a means of cost-cutting.

#### **D. Efficiency**

In spite of the aforementioned differences, there are some acknowledged similarities between PM and CER. One such similarity is that both strategies are aimed at the elimination of inefficiency in medical treatment. The 2009 report cites inefficiency in spending of federal funds for medical care as one of the primary motivations for CER.<sup>37</sup> Similarly, the goal of PM is to discover which medical treatments are best tailored to the individual, and the most tailored treatment is by definition the most effective treatment.

In addition to enhancing efficiency at the clinical level, both PM and CER have the potential to enhance efficiency in medical product development. A corollary to finding the best medical treatment for an individual, in the case of PM, or a subgroup, in the case of CER, is that the best treatment is discovered as early as possible. The early detection of special effectiveness during a clinical trial is most certainly preferable to discovery after years of usage, or worse, after FDA rejection based on ineffectiveness in patients as a whole. Furthermore, both strategies could help to narrow clinical trials to groups which are actually relevant for a particular drug or medical product, saving time

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<sup>36</sup> See Philip R. Reilly, *Personalized Medicine and Pharmacogenomics: New Tools for Disease Management*, 5 DISEASE MANAGEMENT 69 (2004).

<sup>37</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 11.

and resources on superfluous study populations.<sup>38</sup> Thus successful implementation of both PM and CER may enhance efficiency at the product development level and at the clinical level.

### **E. Health Information Technology (HIT) Infrastructure**

The most striking similarity between CER and PM is their demand for the establishment of HIT infrastructure. Both programs rely upon the accumulation and dissemination of substantial amounts of data related to clinical outcomes in individual patients, ranging from genetic to socioeconomic factors. This goal is stated expressly in the second mandate for the FCC, and is implied in any reasonable definition of PM. Indeed, the arrival of genetic databases, starting with the Human Genome Project, is largely responsible for the emergence of PM.<sup>39</sup>

## **IV. INSTITUTIONAL COMPETENCE**

Although many FDA officials are responsible for literature comparing CER to PM, few works have discussed the effect of CER on PM at the FDA specifically. There is a significant amount of study on CER's applicability to clinical trial design, but most of the discussion is centered on scientific or theoretical concepts rather than practical implementation at the FDA.<sup>40</sup> Furthermore, the modern FDA is largely perceived to be

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<sup>38</sup> The FDA has recognized the value of PM in expediting product development through the CPI. The program was launched in response to concerns in the worsening trends of drug development efficiency, and developed into a mechanism for applying PM techniques to the pre-market process. See HHS & FDA, *supra* note 10, at 8.

<sup>39</sup> Although personalized medicine currently encompasses factors not found in large databases, such as culture and lifestyle, originally it stemmed from the recognition that genetic differences have an impact on drug response. The use of genetic factors to tailor medical treatment, pharmacogenomics, is perhaps the most widely recognized branch of personalized medicine. See Reilly, *supra* note 36, at 39.

<sup>40</sup> Most of the literature discusses the potential for CER in improving clinical study design, but does not actually make predictions as to how the FDA will use information from CER, or about how CER studies will interact with clinical studies. See e.g., Alan M. Garber et al., *Does Comparative-Effectiveness*

involved in pre-market research, while current CER studies are designed to test products and strategies that have already been approved.<sup>41</sup> Therefore it is not immediately obvious that the FDA will have any role to play in CER, or that CER will impact the FDA. If the FDA is to become involved with CER, two threshold conditions must be satisfied: 1) the FDA must have legal jurisdiction over the goals of CER and 2) Congress must have intended for the FDA to play a role in CER.

### **A. FDA Jurisdiction**

Legal jurisdiction is unlikely to present a barrier to the FDA's involvement with CER given that the broad scope of the FDA's congressionally delegated mission:

1. Promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;
2. with respect to such products, protect the public health by assuring that [they are not adulterated or misbranded].<sup>42</sup>

One potential limitation is that these goals encompass only certain "regulated products," including drugs, biologics, and medical devices, and might not extend to the "services and procedures" covered by CER. Under the off-label use doctrine, physicians may employ FDA approved drugs, biologics, or medical devices for uses other than those that have been approved.<sup>43</sup> Thus, even if CER could prove a drug to be more beneficial in certain situations, the FDA would have limited power to enforce the preferred uses of the drug over all other possible uses.

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*Research Threaten Personalized Medicine?* 360 NEW. ENG. J. MED. 1925 (2009) (discussing the problems with current clinical studies and explaining why CER will generate study designs which could advance PM in general).

<sup>41</sup> See Agency for Healthcare Research and Quality: Effective Health Care Program, <http://www.effectivehealthcare.ahrq.gov/index.cfm> (last visited Mar. 8, 2010) (referencing proposed studies available for review on the site as of March 2010).

<sup>42</sup> Food, Drug, and Cosmetic Act, §903(b).

<sup>43</sup> "Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm116355.htm> (last visited on Mar. 7, 2010).

Nonetheless, the FDA is not entirely powerless to prohibit unapproved product use. Physicians who choose to employ a regulated product for unapproved uses “have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.”<sup>44</sup> In addition, the FDA can mandate institutional oversight at any point in the process.<sup>45</sup> As to the second goal of CER, aimed at data collection, the FDA is not likely inhibited jurisdictionally. There may be external limitations including privacy laws; however, the FDA embarked upon expansive data collection programs as early as the 1960’s.<sup>46</sup>

The other potential limitation to the FDA’s involvement with CER – namely the post-approval nature of CER studies – is similarly surmountable. Although most of the discussion regarding CER at the FDA has revolved around clinical trials, the FDA is not limited to pre-market research. Historically, the FDA was merely responsible for enforcement actions after the entrance of a food or drug into the market.<sup>47</sup> Only recently has the FDA come to play a determinative role in product development, but it continues to perform a policing function for products that are already out on the market.<sup>48</sup>

## **B. Congressional Intent**

Although the FDA’s legal jurisdiction does not present a bar to involvement with CER, it is possible that Congress did not envision the FDA as a major player in its execution. Through budget appropriations, Congress has imparted primary responsibility

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<sup>44</sup> *Id.*

<sup>45</sup> *See id.*

<sup>46</sup> *See* PETER BARTON HUTT ET AL., FOOD AND DRUG LAW CASES AND MATERIALS 647 (3rd ed. 2007) (explaining that the data monitoring committee was established in the 1960s to collect and organize the “data emerging from large clinical studies to determine whether the study should be stopped . . .”).

<sup>47</sup> *See id.* at 1-27.

<sup>48</sup> *See id.*

for CER to agencies other than the FDA.<sup>49</sup> The National Institutes of Health (NIH) and the Secretary of Health and Human Services (HHS) are the principal recipients, each having been apportioned \$400 million.<sup>50</sup> The agency historically responsible for projects comparing effectiveness of medical treatments is the Federal Agency for Healthcare Research and Quality (AHRQ), which began receiving federal support for comparative clinical effectiveness in 2003.<sup>51</sup> Funding for these efforts has continued to rise steadily, and jumped to \$300 million with the ARRA.<sup>52</sup> The FDA is noticeably absent from the recipient list, which raises doubts as to whether Congress intended for the FDA to be involved at all.

The 2009 report, however, erases such doubts about the exclusion of the FDA from Congress' plan for CER. The report was authored in part by a member of the FDA and explicitly mentions the FDA six times.<sup>53</sup> The first time is in the context of clinical trials, for the purpose of differentiating CER from clinical efficacy studies.<sup>54</sup> The FDA is mentioned twice as playing a role in the “dissemination and translation” of information flowing from CER, once as a resource for expertise on effectiveness trials, and twice for “data infrastructure” development, specifically for the collection of data on “drug and device trials and safety.”<sup>55</sup> Most importantly, the FDA is deeply and inextricably involved in the subject matter addressed by CER.

Frankly, it is hard to imagine how CER – research focused on health outcomes relating to medical treatment – could fail to affect FDA policy and procedure. The real

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<sup>49</sup> See GOODMAN, *supra* note 27, at 3.

<sup>50</sup> See *id.*

<sup>51</sup> See *id.*

<sup>52</sup> See *id.*

<sup>53</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17.

<sup>54</sup> See *id.* at 6.

<sup>55</sup> *Id.* at 39, 41, 47, 68.



question is how the FDA will interact with other public and private actors in the implementation of CER. Of the two dominant actors in the arena of pre-market approval – the FDA and the PTO – it is not clear that the FDA should have primary responsibility for implementing the goals of CER. In light of the ever-increasing backlog of patent applications, some have suggested enhancing the policing function of the PTO in eliminating applications which do not represent a significant improvement over the prior art.<sup>56</sup> The problem is especially apparent in the pharmaceutical industry, where seventy-seven percent of drugs approved between 1998 and 2002 are “me-too” drugs, which do not provide any significant benefit over other drugs in the market.<sup>57</sup>

In addition to the PTO, Congress may have intended for the private sector to play a significant role to play in research and data accumulation. Many patients are reluctant to submit themselves to clinical research, but being a test subject becomes less frightening from the local general practitioner’s office. Advocates of PM have recognized private sector involvement by emphasizing the role of “multidisciplinary teams” including “behavioral and social scientists, medical ethicists, policy experts, mathematicians, physical and biological scientists,” just to name a few of the key players.<sup>58</sup>

Fortunately, the FCC was “established ... to foster optimum coordination of CER conducted or supported by Federal departments and agencies.”<sup>59</sup> With the counsel of the FCC, the FDA could conceivably become a very active player in the development of

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<sup>56</sup> See e.g., MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* 89-91 (Random House 2004).

<sup>57</sup> See *id.*

<sup>58</sup> Muin J. Khoury et al., *Comparative Effectiveness Research and Genomic Medicine: An Evolving Partnership for 21<sup>st</sup> Century Medicine*, 11 *GENETICS IN MEDICINE* 707, 710 (2009).

<sup>59</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 73.

CER. Three areas in particular have been suggested in the literature as feasible means of accommodating CER: clinical studies, information dissemination, and database accumulation. The remainder of the paper will explore how the theoretical differences – cited in literature which compares CER to PM generally – will play out in the implementation of CER at the FDA in these three areas.

## **V. CER AT THE FDA**

### **A. Clinical Trials**

To date, the FDA has not made significant progress towards PM in clinical trial design.<sup>60</sup> The guidelines merely create the opportunity for data submission on pharmacogenomic data, but as of 2007, only thirty submissions had been filed under this procedure, most of which were suggestions for improvement of clinical study design.<sup>61</sup> Rather, the current procedures for clinical testing have arguably stunted the growth of PM. A recent article went so far as to say that “the greatest obstacle to the adoption of personalized approaches such as genomic testing . . . is the lack of adequately designed studies assessing their clinical utility . . . .”<sup>62</sup>

In the case of Iressa, researchers were immediately able to rationalize the effectiveness disparity among subgroups because the distinction was drawn upon racial lines and the relevant mutation is of a common protein known to play a role in the drug’s

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<sup>60</sup> See e.g., Emily Singer, *Personalized Medicine Prompts Push to Redesign Clinical Trials*, 11 NATURE MEDICINE 462 (2005) (“clinical trials . . . fail to take advantage of continuing advances in pharmacogenomics.”).

<sup>61</sup> See Goodsaid, *supra* note 9, at 355.

<sup>62</sup> Garber, *supra* note 40, at 1926.

activity.<sup>63</sup> However, such disparities may be very difficult to recognize in the context of a randomized controlled trial, and perhaps even more difficult to rationalize.<sup>64</sup>

Given that there is significant room for improvement, it is in the area of clinical study design that CER may hold the most promise for the furtherance of PM. Through extremely large-scale studies, CER offers the “power to investigate effects at the subgroup level that often cannot be determined in a randomized trial.”<sup>65</sup> CER studies might also include factors which have been neglected by the FDA’s current efforts to implement personalized medicine.<sup>66</sup> The 2009 report emphasizes that CER is intended to investigate a broad array of factors related to medical treatment, ranging from “linguistic and cultural attributes” to diet and environment – precisely the types of factors for which personalized medicine is intended to account.<sup>67</sup> Should CER not achieve its lofty goals of subgroup inclusion and superior study design, however, it also has the potential to pull clinical trials in the opposite direction, away from PM.

### *1. Efficiency*

Pre-market approval through clinical trials is at the heart of the FDA’s current mission, and the agency is necessarily focused on resolving inefficiencies that occur before a product is released into the market.<sup>68</sup> In contrast, CER is motivated by a concern for efficiency at the clinical, or “real-world” level.<sup>69</sup> Nonetheless, the goals of the two

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<sup>63</sup> See Iressa, *supra* note 2.

<sup>64</sup> See S.M. Huang & R. Temple, *Is This the Drug or Dose for You?: Impact and Consideration of Ethnic Factors in Global Drug Development, Regulatory Review, and Clinical Practice*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 287 (2008).

<sup>65</sup> FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 6.

<sup>66</sup> See *id.* at 24.

<sup>67</sup> *Id.* at 26.

<sup>68</sup> See HUTT, *supra* note 46, at 1-27.

<sup>69</sup> FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 16.

programs could perhaps overlap symbiotically to enhance efficiency at the FDA in at least three ways.

First, lessons learned from the design of CER studies could be incorporated into FDA clinical trials. Currently little is known about optimal study designs for discovering disparities in effectiveness, but “these are precisely these kinds of issues that CER is designed to address.”<sup>70</sup> FDA can benefit from this knowledge in crafting its own clinical study designs. Secondly, the scientific information gleaned from CER could enhance efficiency in FDA clinical trials by providing generalized information about relevant subgroups for various types of medical treatments. For example, if a pharmaceutical company knows from CER studies that a particular genre of drug is likely to be more effective in a particular subgroup, then it can initiate clinical studies on only that subgroup. Finally, CER might improve the quality of new product applications received by the FDA by incentivizing development of products which represent significant improvements over current treatment options. Hopefully, large scale implementation of CER will stem the tide of “me-too” drugs, those which do not provide any significant advantage over prior art.<sup>71</sup> In this way CER may create a wider variety of opportunities for medical regimes that are genuinely different.

Such potential for overlap raises the concern that FDA clinical trials and the CER initiative might render either one or the other superfluous. Why undergo any clinical trials when more rigorous testing of the same nature is required in the future? Or, on the other hand, why require post-release testing when the FDA already has incorporated all elements of that testing into its approval requirements? The answer to this question

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<sup>70</sup> Garber, *supra* note 40, at 1926.

<sup>71</sup> See ANGELL, *supra* note 56, at 75.

depends largely upon the coordination efforts of the FCC. Regardless of efforts to assess efficiency after market release, however, clearly some study will be necessary prior to market release. The FCC and the FDA will simply have to struggle with where to draw the line between studies which must be completed prior to release and those which must be completed subsequent to release.

## *2. Financial considerations*

CER's opponents highlight the paramount importance of financial considerations in the shaping of related legislation and regulatory programs.<sup>72</sup> Most of these concerns arise out of a fear that insurance coverage decisions – particularly of government health insurance programs – will be based on this research. While the FDA's pronouncements may affect coverage decisions, regulation of such decisions is beyond the jurisdictional reach of the FDA.<sup>73</sup> FDA determines which drugs, biologics, and medical devices are released onto the market, but can only indirectly affect who receives those products through labeling and the media.<sup>74</sup>

Quite to the contrary, the financial motivations driving CER could spur PM research in ways that benefit the FDA. Drug development is already an incredibly expensive venture;<sup>75</sup> imposing additional costs on the industry by requiring the testing of relative effectiveness could seriously disincentivize drug development. Currently the private sector bears the expense of costly FDA clinical trials, but hopefully the apportionment of federal funds to CER will allow the public to reap the benefits of such

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<sup>72</sup> See AMERICAN ACADEMY OF ACTUARIES, *supra* note 35, at 4.

<sup>73</sup> See HUTT, *supra* note 46, at 28.

<sup>74</sup> See *id.*

<sup>75</sup> See e.g., Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really \$802 Million?* 25 HEALTH AFF. 420, 420 (2006) (estimating the total cost of drug development to be \$868 million).

studies without imposing the costs on private industry. Concededly most CER studies are envisioned to occur subsequent to FDA approval;<sup>76</sup> however as mentioned above, CER studies have the potential to enhance pre-market clinical trials through the development of improved study designs and by providing information about relevant subgroups.

### *3. Prospective v. Retrospective*

As explained above, synergy between CER and PM in clinical trials is dependent upon the accuracy of CER in identifying relevant subgroups and assessing a treatment's effectiveness in those subgroups. The previous failures of the FDA to assess relative effectiveness in clinical trials raise doubts as to whether prospective studies of any kind are capable of this feat. Some of the reasons for current deficiencies in FDA clinical study design include small data samples, underrepresentation of demographic subgroups, and an inability to account for currently "unrecognized genetic or physiologic pharmacodynamic" differences.<sup>77</sup> The 2009 report additionally criticizes FDA clinical trials for their failure to assess "real-world" clinical utility.<sup>78</sup> Consequently, it comes as no surprise that according to the Secretary's Advisory Committee on Genetics and Health in Society, most attempts at personalizing medicine via genomic testing have not been clinically successful.<sup>79</sup>

Certainly CER analysis will run into the same problems that the FDA has encountered in attempting to alter clinical trials to incorporate PM. Retrospective PM

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<sup>76</sup> See Agency for Healthcare Research and Quality, *supra* note 41.

<sup>77</sup> See Huang, *supra* note 64, at 290.

<sup>78</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 4 (contrasting current FDA efficacy trials, which aim to determine whether a drug will be "efficacious under ideal conditions" with CER, which aims to acquire data incorporating variables existing in the "real world.").

<sup>79</sup> See Secretary's Advisory Committee on Genetics and Health in Society, *US System of Oversight of Genetic Testing: A response to the Charge of the Secretary of HHS*, April 2008, [http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS\\_oversight\\_report.pdf](http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf) (last visited Mar. 8, 2010).

studies have the advantage of years of clinical data, which may prove to be necessary. Effectively, CER may be attempting to impose a prospective framework onto a field that may not be capable of accommodating it.

Presumably many of the obstacles encountered by the FDA are not entirely insurmountable. Perhaps the missing link between retrospective and prospective studies is merely technological advancement. Increased federal funding for CER may decrease development costs to some extent, and the accumulation of databases should bring costs back down after an initial period of sharp increase. In light of the resources – in both money and time – being poured into CER, there is at least some hope that it will be successful in assessing true relative effectiveness among subgroups in a prospective manner.

#### *4. Group v. Individual*

This putative conflict implicates the same issues that exist for the retrospective/prospective conflict described above. Essentially, there is no conflict in the event that CER is actually able to identify subgroups relevant for a medical treatment and compare them accurately, *i.e.*, as long as CER actually accomplishes its stated goals. Given the history of CER, which has not been terribly diligent in its inclusion of subgroups, the outlook appears fairly bleak for PM. According to a study conducted by the Congressional Research Service, only thirteen percent of comparative clinical effectiveness studies published in the peer-reviewed literature during the period between January 2004 and August 2007 analyzed variation in effectiveness for subpopulations other than white middle-age adults.<sup>80</sup> Concededly, a cursory review of the AHRQ's

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<sup>80</sup> G.A. JACOBSON, COMPARATIVE CLINICAL EFFECTIVENESS AND COST-EFFECTIVENESS RESEARCH: BACKGROUND, HISTORY, AND OVERVIEW (2007).

website evinces an intent to move in the direction of greater subgroup inclusion. Of the six proposed research studies available for comment, all suggest a list of relevant subgroups for comparative study.<sup>81</sup> These subgroups all involve distinctions based on age, gender, ethnicity, and health status relative to the treatment at issue.<sup>82</sup>

An additional snag implicated by this conflict is CER's emphasis on racial subgroups, which may make correct group identification even more difficult. Many of CER's concessions to PM advocates from the 2009 report involve the guarantee that racial subgroups will be considered in CER studies. In fact, one of the stated goals of the report is to include previously underrepresented ethnic subgroups in CER studies. While this appears to be a laudable goal, both in furtherance of CER and in FDA clinical trials, significant complications result from using self-identified racial subgroups for scientific analysis, particularly in the field of genetics.

A glance at the current list of approved biomarkers reveals the limited relevance of racial distinctions. Fewer than half of genetic disparities in drug response are a consequence of ethnicity.<sup>83</sup> Although racial distinctions are the most easily observed and thus might be the most logical choice for a clinically relevant biomarker, a large body of scientific scholarship exists that discounts the genetic relevance of race. First of all, race is not a well-defined genetic category; rather it is a continuum. "One's ethnicity/race is, at best, a probabilistic guess at one's true genetic makeup."<sup>84</sup> In 1999, no less an authority than the Institute of Medicine stated that race could no longer be considered a "biological reality" but was instead a "construct of human variability based on perceived

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<sup>81</sup> See Agency for Healthcare Research and Quality, *supra* note 41.

<sup>82</sup> See *id.*

<sup>83</sup> See Huang, *supra* note 64, at 292 tbl. 1.

<sup>84</sup> P.C. Ng et al., *Individual Genomes Instead of Race for Personalized Medicine*, 84 CLINICAL PHARMACOLOGY & THERAPEUTICS 306, 306 (2008).



differences in biology, physical appearance, and behavior.”<sup>85</sup> Thus as the cost of genome sequencing continually falls, it may become unnecessary to use racial distinctions as a proxy for real genetic differences.

The foregoing analysis is not intended to discount the clear advantages of including racial minorities in clinical trials. Greater diversity in the test population can provide results that are more individualized, and greater diversity in ethnicity in particular can contribute information about cultural factors in medicine. The FDA will have to be vigilant, however, in applying principles gleaned from CER to clinical trials.

### **B. Information Dissemination**

Successful integration of PM and CER depends upon the communication of study results to the public in “an accurate, comprehensible manner” that includes study limitations.<sup>86</sup> Patients cannot make health care decisions for themselves as individuals without access to information about treatment efficacy. Hence none of the aforementioned theoretical conflicts between PM and CER poses an obstacle in the area of information dissemination; in this regard, the two strategies are perfectly aligned.

Most of the concerns with CER – prospectivity and the group/individual distinction – are centered on study design, which is not affected by information dissemination. Financial considerations may drive what kinds of information reach the public, and thus PM advocates could argue that the government might impede PM by selectively disclosing information about large populations rather than subgroups. This scenario seems unlikely, however, given the FCC’s explicit emphasis on subgroup

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<sup>85</sup> Sandra Soo-Jin Lee et al., *The Meaning of Race in New Genomics: Implications for Health Disparities Research*, YALE JOURNAL OF HEALTH POLICY, LAW, & ETHICS 33, 38 (2001).

<sup>86</sup> GOODMAN, *supra* note 27, at 20.

assessment<sup>87</sup> and the multitude of safeguards against secrecy in administrative policy-making.<sup>88</sup> There remains the potential for inefficiency through duplicative efforts, but such redundancies could be eliminated through coordination by the FCC.

Fortunately, the optimal infrastructure for information dissemination already exists at the FDA in the form of labeling requirements. The 2009 report repeatedly emphasizes the patient-oriented nature of CER, focusing on decisions at the level of the patient-doctor relationship.<sup>89</sup> What more direct and effective way to reach both physicians and patients than labeling? Since the FDA has already established a very structured approach to labeling through decades of experience, inclusion of CER data on product labels would be a natural progression. Such directions would serve to enhance both PM and CER by tailoring decisions to the individual patient. Additionally, publicity is one of the FDA's most powerful assets;<sup>90</sup> thus it seems that the FDA is particularly well equipped to disseminate information to the public.

### **C. Database Accumulation**

Another explicit area of overlap between the goals of PM and CER is in the field of database accumulation. Commentators universally acknowledge the paramount importance of the creation of an infrastructure to support health information technology (HIT), both for PM and for CER.<sup>91</sup> Such information could alleviate some of the

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<sup>87</sup> See e.g., FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 5, 13 & 16.

<sup>88</sup> In response to concerns about nondelegation and secrecy, Congress passed the Freedom of Information Act and the Government in the Sunshine Act to ensure that administrative proceedings were subject to review by the public. See PETER L. STRAUSS ET AL., GELLHORN AND BYSE'S ADMINISTRATIVE LAW CASES AND COMMENTS 733 & 762 (10th ed. 2003).

<sup>89</sup> See FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 10-11.

<sup>90</sup> See HUTT, *supra* note 46, at 1344. The FD&C Act "expressly authorizes the issuance of information to the public." *Id.*

<sup>91</sup> See e.g., GOODMAN, *supra* note 27, at 19.

problems inherent in clinical trials by significantly increasing the population data set and hopefully by providing information about relevant subgroups.

Use of data accumulation in CER could actually minimize the conflict between PM's retrospective nature and CER's prospective goals by incorporating a retrospective aspect into CER and enhancing the prospectivity of PM. The (possibly) semantic distinction between group and individual is not present in legislative and administrative documents discussing data collection, as both strategies require information about medical outcome in individuals.<sup>92</sup> Financial considerations might affect the kind of data acquired for CER, but it is hard to imagine how data collection could hinder PM – a science based largely on genetic databases.<sup>93</sup> Perhaps the greatest danger is that the data gathering efforts of the FDA and the FCC will overlap, wasting government resources with duplicative efforts. However it is easier to merge information from various agencies than to coordinate research projects among agencies, and the FCC is indubitably capable of the task.

The FDA has already begun data accumulation efforts in furtherance of PM, beginning in May 2008 with the launch of the Sentinel Initiative.<sup>94</sup> The goal of the program is to create an electronic database which contains information about patient

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<sup>92</sup> Data collection efforts at the FDA, beginning with the Data Monitoring Committee in the 1960's, was as an attempt to determine when clinical trials should be stopped. *See* HUTT, *supra* note 46, at 647. Data about clinical trials is, by definition, data about individual results. More recent efforts, including the Sentinel initiative, attempt to collect data after market release but are similarly inherently focused on results in individual patients. *See* Food and Drug Administration, FDA's Sentinel Initiative, <http://www.fda.gov/Safety/FDASentinelInitiative/default.htm> (last visited Apr. 9, 2010). Similarly, the FCC is instructed to disseminate information generally from CER studies, which intrinsically involves information about individuals. *See generally* FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17.

<sup>93</sup> Although pharmacogenomics, the study of the effects of genetics on drug response, is only a branch within PM, as mentioned above it is at the heart of PM and is largely responsible for its emergence. *See* Reilly, *supra* note 36, at 69.

<sup>94</sup> *See* FDA's Sentinel Initiative, *supra* note 92.

response to drugs, biologics, and medical devices.<sup>95</sup> Janet Woodcock has been an outspoken supporter of electronic health record (EHR) collection in furtherance of PM.<sup>96</sup> In fact, she believes that CER and PM can work together to gather information from the community rather than the research lab, thereby collecting greater amounts of more pragmatic data.<sup>97</sup>

Infrastructure suggested as part of CER aligns perfectly with this design. For instance, one of the four goals of CER as stated in the 2009 report is to develop a “distributed practice-based data network, longitudinal linked administrative or Electronic Health Record (EHR) databases, or patient registries.”<sup>98</sup> The FDA and the FCC have only presented sparse sketches describing the shape of this infrastructure, but it is hard to imagine how the accumulation of information could thwart either PM or CER.

## VI. CONCLUSION

In spite of certain ideological and motivational differences in PM and CER, their practical implementation by the FDA has the potential to be symbiotic. The general consensus in the literature seems to be that the ideological gap can be bridged, but that careful vigilance will be necessary to ensure that CER does not lead the FDA astray from its stated goal of furthering PM.<sup>99</sup> The two main obstacles to the practical implementation of CER alongside PM at the FDA are scientific constraints on study design and coordination difficulties. The FDA has been actively working to implement PM since its inception; if FDA has failed to identify subgroups and assess relative

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<sup>95</sup> *See id.*

<sup>96</sup> *See* Turna Ray, *Comparative Effectiveness Research and Personalized Medicine*, PHARMACOGENOMICS REPORTER, Nov. 4, 2009, <http://www.genomeweb.com/dxpgx/comparative-effectiveness-and-personalized-medicine-can-unite-community-based-re?page=show>.

<sup>97</sup> *See id.*

<sup>98</sup> *See* FEDERAL COORDINATING COUNCIL FOR COMPARATIVE EFFECTIVENESS, *supra* note 17, at 6.

<sup>99</sup> *See* GOODMAN, *supra* note 27, at 24.

effectiveness, why should CER succeed? The second major concern is that the data collection and information dissemination functions of the other agencies implementing CER will overlap with those at the FDA. Nonetheless, given the widespread and growing concern for the preservation of PM, it is unlikely that the FDA will be hindered by CER in its quest for the furtherance of PM.